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Original Contribution

Is Cognitive Aging Predicted by One's Own or One's Parents' Educational Level? Results From the Three-City Study

M. Maria Glymour*, Christophe Tzourio, and Carole Dufouil

* Correspondence to Dr. M. Maria Glymour, Department of Society, Human Development, and Health, Harvard School of Public Health, Kresge 617, 677 Huntington Avenue, Boston, MA 02115 (e-mail: mglymour@hsph.harvard.edu).

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The authors examined the associations of participants' and their parents' educational levels with cognitive decline while addressing methodological limitations that might explain inconsistent results in prior work. Residents of Dijon, France ($n = 4,480$) 65 years of age or older who were enrolled between 1999 and 2001 were assessed using the Isaacs' verbal fluency test, Benton Visual Retention Test, Trail Making Test B, and Mini-Mental State Examination up to 5 times over 9 years. The authors used random-intercepts mixed models with inverse probability weighting to account for differential survival (conditional on past performance) and quantile regressions to assess bias from measurement floors or ceilings. Higher parental educational levels predicted better average baseline performances for all tests but a faster average decline in score on the Isaacs' test. Higher participant educational attainment predicted better baseline performances on all tests and slower average declines in Benton Visual Retention Test, Trail Making Test B, and Mini-Mental State Examination scores. Slope differences were generally small, and most were not robust to alternative model specifications. Quantile regressions suggested that ceiling effects might have modestly biased effect estimates, although the direction of this bias might depend on the test instrument. These findings suggest that the possible impacts of educational experiences on cognitive change are small, domain-specific, and potentially incorrectly estimated in conventional analyses because of measurement ceilings.

bias (epidemiology); cognitive disorders/dementia; cognitive reserve; cohort studies

Abbreviations: BVRT, Benton Visual Retention Test; IPW, inverse probability weight; MMSE, Mini-Mental State Examination; TMTB, Trail Making Test B.

Editor's note: *An invited commentary on this article appears on page 760, and the authors' response is published on page 762.*

Prior research has suggested that both a person's own educational attainment or duration of schooling and that of his/her parents affect the risk of cognitive impairment and dementia in the later years (1–12). There has been little research on the association between parental educational level and the rate of cognitive decline, however, and findings regarding one's own education and cognitive change have been mixed. Results from several early studies suggested that education slowed the rate of cognitive decline (13), which was consistent with the theory of cognitive reserve. However, these results were challenged by subsequent reports in which improved longitudinal methods were used (14–20). Some recent analyses found that individuals with higher levels of education or socioeconomic position experience accelerated cognitive decline, at least in some domains or age groups (15, 16, 21). Although this surprising result has been largely regarded as spurious, we consider 3 possible explanations for the association.

First, education might predict accelerated cognitive aging if cognitive skills developed through education are early targets of neurodegenerative or cerebrovascular disease. For example, individuals with high levels of education are more likely to deploy explicit strategies in verbal fluency

and verbal memory tests (22, 23). These strategies are associated with recruitment of specific cortical regions, for example, the dorsolateral prefrontal cortex (24). Cortical networks or regions underlying strategy use may be affected relatively early in the development of neurodegenerative diseases (25). If so, highly educated individuals may be differentially affected and decline more quickly than others, especially in strategy-dependent domains.

Second, education might predict accelerated cognitive decline under a ''last in, first out'' model, in which more recently developed cognitive skills are lost earliest as age-related neurologic disease develops. This explanation suggests that factors that influence cognitive skills early in life, for example, parental education, would be less strongly associated with cognitive decline than factors affecting later cognitive development, such as one's own education.

Finally, although education is generally considered salubrious, it could increase the risk of neurologic disease via behavioral or physiologic changes. This seems unlikely given prior evidence about the health effects of education, but it cannot be ruled out. We examined relations between one's own and parental education and the rates of decline in 4 domains of cognitive function in a French cohort, using methods to help address methodological limitations that might explain inconsistent results in prior work.

MATERIALS AND METHODS

Data

The Three-City Study, a population-based prospective study of the elderly in Bordeaux, Montpellier, and Dijon, France, has previously been described in detail (26). We report here results from Dijon only, the site at which parental educational levels were assessed. Participants ($n = 4{,}931$) were enrolled between January 1999 and March 2001 from a sample of noninstitutionalized individuals who were 65 years of age or older and randomly selected from city electoral rolls. Baseline interviews were conducted at participants' homes by trained psychologists. Follow-up interviews were conducted approximately 2, 4, 7, and 9 years after enrollment (through February 2010). The study protocol was approved by the ethical committee of the University Hospital of Kremlin-Bicêtre, and all subjects signed legal consent forms. We excluded 68 individuals with diagnosed dementia at baseline, 2 with unknown educational levels, and 381 for whom we were missing one or more baseline cognitive assessments.

Measures

Educational levels of participants and their parents were reported at baseline. Maternal and paternal education levels were highly concordant, but when they differed, we used the minimum value dichotomized as primary or no school versus secondary school or more. An alternative specification using father's educational level showed similar results. We retained 437 respondents who did not report parental educational level in the analyses, identifying them in a separate category with an indicator variable.

The highest level of education for each participant was modeled as a dichotomous variable that indicated either secondary level education without a diploma (9–12 years) or higher. This approximated the sample median; sensitivity analyses using education as an ordered variable (1–6) had qualitatively similar results.

At each wave, cognitive testing was conducted using 3 tests: Isaacs' test of verbal/category fluency (hereafter referred to as the ISAAC; associated with both literacy and the ability to organize thinking by clustering words) (27), the Benton Visual Retention Test (BVRT; used to assess nonverbal memory and associated with construction and design copying tasks) (28), and the Mini-Mental State Examination (MMSE; a general screening instrument for dementia thought to briefly assess 5 domains: working memory, language and praxis, orientation, memory, and attention) (29). Trail Making Test B (TMTB) (30) was used only at baseline and years 4, 7, and 9. Trail Making Test performance is influenced by attention, visuomotor tracking and speed, divided attention, and cognitive flexibility (31). TMTB scores were calculated as the ratio of time to task completion divided by the number of correct connections. We reversed coding for TMTB by multiplying all coefficients by -1. Therefore, in all models, a positive coefficient indicated better performance. To reduce the influence of outlying values, time was capped at 300 seconds and total score was capped at 35 (the 99th percentile at baseline). To provide consistent scaling, each test result was converted to a z score using the baseline mean and standard deviation for that instrument. We created cognitive summary scores by adding the z scores for ISAAC, BVRT, and MMSE; TMTB was excluded from the summary because it was not assessed in year 2. Extreme values were eliminated by recoding any values more than 3 standard deviations above or below the mean as a z score of 3 (or -3). Models were adjusted for sex, age at baseline (recentered so a value of 0 represented age 65 years), and years of follow-up since the baseline assessment. Models for participants' own educational levels were adjusted for parental educational levels because parents' education temporally precedes and probably affects participants' own education. Models showing education estimates without adjustment for parental educational level are available from the authors.

Analyses

We used random-intercept growth curve models to examine the relation between each exposure and level and the rate of change in cognitive outcomes. To account for practice effects, we included indicators for first test encounter in all models. If performance improves with repeated testing, we would expect this indicator to have a negative coefficient. To illustrate the functional form for rate of change over follow-up, we first plotted predicted trajectory of the summary score from a model that included baseline age (centered at 65 years), baseline age squared, years of follow-up (i.e., years since baseline assessment), years of follow-up squared, first test encounter indicator, and sex.

We next estimated the annual rate of change for each cognitive test in linear models, dropping quadratic terms

for clarity of interpretation. These models were adjusted for baseline age, years of follow-up, indicator for first test encounter, sex, and interviewer. We interpreted coefficients for years of follow-up as the primary indicators of rate of cognitive aging, but coefficients for baseline age are also shown because they are often more precisely estimated (32). Similar coefficients suggest minimal cohort effects. In such cases, a combined coefficient for ''current age'' may be a preferable quantification of the rate of cognitive aging (32), and models based on current age are shown in Web Table 1 (available at http://aje.oxfordjournals.org/).

To assess the impact of each education variable on the rate of cognitive change, we repeated the mixed models and included interactions between baseline age and educational level, years of follow-up and educational level, and the first test encounter indicator and educational level. We report both the main associations for educational level (representing the predicted baseline difference in cognitive level between high- and low-education groups, for individuals enrolled at age 65 years) and the interactions of educational level and years of follow-up (representing differences in rate of change over follow-up). Models included the interaction of the practice effect with education to allow for educational differences in practice effects. We found no evidence that men and women differed with respect to practice effects or annual rates of change, so we estimated pooled models.

We repeated primary results using quantile regression models for the 20th–80th quantiles. Conventional linear models contrast the mean outcome value among exposed versus nonexposed participants, whereas quantile q regression coefficients contrast the qth quantile of the outcome among exposed versus nonexposed participants. We estimated the education main effect (corresponding to predicted value at baseline assessment for a respondent age 65 at baseline) and education $\times$ years of follow-up quantile regression coefficients, adjusting for nearly the same covariates as in the primary linear mixed models. Quantile regression models were not adjusted for interviewer indicator variables because of estimation problems.

We first examined the results of quantile regression models for evidence of substantial ceiling or floor effects. Regression coefficients for baseline level at high quantiles that are much smaller than coefficients at low quantiles suggest that ceiling effects are compressing differences among high-functioning individuals. Such ceilings may bias the estimated impact on rate of change either up or down if some people improve their performance over time. Regression coefficients at low quantiles will often be more robust to ceiling effects than mean regression coefficients, provided that within covariate strata, the quantile is below the ceiling. Therefore, when there was evidence of possible ceiling effects, we focused our interpretation on the lower quantile regression coefficients. We provide approximate tests of statistical significance for quantile regression coefficients based on bootstrapped (200 repetitions) variance estimates inflated by a factor of 3.3 to account for repeated measures on the same respondent. The design effect of 3.3 was estimated based on design effects observed for linear models.

Because of potential bias induced by selective survival and loss to follow up in studies of determinants of cognitive aging, we used inverse probability weights (IPWs) to account for selective loss to follow-up or death (33–37). IPWs were estimated using logistic regressions predicting the probability of surviving to each wave (given that the respondent survived to the prior wave) and the probability of completing each cognitive assessment (given that the respondent survived to the current wave and completed the cognitive assessment in all prior waves). The models were estimated for each wave based on all covariates in the primary analytic models, as well as lagged values of each cognitive score, Centers for Epidemiologic Studies—Depression score, and self-rated health. The final IPW was the product of the survival IPW (the inverse of the predicted probability from the model for surviving) and the completion IPW (the inverse of the predicted probability of completing the cognitive assessment). We stabilized these weights using the probability of being observed predicted with only time-constant covariates in the numerator. Analyses used SAS, versions 9.1 and 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Among the 451 (9.1%) persons excluded from the analytic sample, the primary reason for exclusion was missing information on baseline TMTB score ($n = 284$). The final analytic sample included 4,480 individuals (Table 1).

Scores on all 4 cognitive tests were worse at first test encounter and in respondents who were older at baseline, and they declined across years of follow up (Table 2). The coefficients for the rate of change over follow-up in weighted models indicated a faster decline than did coefficients based on unweighted models for all 4 outcomes. In weighted models, the coefficient for baseline age was identical to the coefficient for years of follow up only for the ISAAC. Models of the trajectory of mean summary score (ISAAC, BVRT, and MMSE) based on a flexible quadratic functional form showed a largely consistent pattern (Figure 1, solid line), with substantial impairment in performance at first assessment followed by a slow decline over years of follow-up. The median summary score (Figure 1, middle dashed line) was slightly better than the mean summary score, but the trajectory of median performance nearly mirrored the trajectory of the mean performance. The 80th and 20th percentiles followed similar patterns of change over time.

Higher parental educational level was associated with better predicted scores at baseline assessment (shown for age 65 years) for all 4 tests (Table 3). Higher parental educational level predicted faster decline during follow-up on the ISAAC ($\beta = -0.013$; 95% confidence interval: -0.022, -0.003) but no significant difference for other measures. The coefficient for the interaction of baseline age and parental educational level was nearly identical to the coefficient for the interaction of baseline age and years of follow up in the model predicting ISAAC score (-0.016 vs. -0.013). In the ISAAC, parental educational level was associated with an initial level advantage 47 times the magnitude of the disadvantage in the rate of change (in other words, the faster rate of decline would be expected to offset the better initial position after 47 years).

Table 1. Characteristics of the Baseline Sample in the Three-City Study, Dijon, France, 1999–2001

	Included			Excluded			*P* Value[a]
	No. of Participants	%	Mean (SD)	No. of Participants	%	Mean (SD)	
Total	4,480	100		451	100		
Age at baseline			74.3 (5.5)			78.0 (7.0)	<0.01
Male sex	1,721	38		167	37		0.56
Parents' educational level							<0.01
Primary school or less	3,381	75		294	65		
Secondary school or more	662	15		55	12		
Not reported	437	10		102	23		
Participant's educational level							<0.01
None	83	2		40	9		
Primary school (<6 years)	1,427	32		174	39		
Middle school (6–8 years)	718	16		72	16		
Short technical or professional degree (8–9years)	743	17		58	13		
Secondary school (9–12 years)	563	13		46	10		
Higher technical or professional degree[b]	946	21		57	13		
Baseline score on cognitive tests[c]							
Verbal fluency			12.3 (2.6)			9.6 (3.1)	<0.01
Trail Making Test B, raw (seconds to completion)			111.6 (49.4)			214.3 (96.4)	<0.01
Trail Making Test B, corrected[d]			6.8 (5.7)			12.9 (10.1)	<0.01
Benton Visual Retention Test			11.4 (2.0)			9.1 (2.8)	<0.01
Mini-Mental State Examination			27.5 (1.8)			24.9 (3.3)	<0.01

Abbreviation: SD, standard deviation.
[a] *P* values for the null hypothesis that included respondents did not differ from those for the null hypothesis that excluded respondents.
[b] Corresponding to enseignement technique ou professionnel long ou Enseignement supérieur, y compris technique supérieur.
[c] Before standardization.
[d] Seconds to completion divided by correct connections.

Adjusted for parental educational level, participants' own educational attainment was associated with a higher predicted baseline level on all outcomes. Participants' own education was not significantly associated with rate of decline on the ISAAC, but it predicted slower rates of performance declines in the BVRT, TMTB, and MMSE. Results were similar in models that were not adjusted for parental education (not shown), except that high participant education was significantly associated with a faster decline in ISAAC score. Results based on current age (Web Table 1) similarly suggested that participants' own educational levels predicted a faster decline on the ISAAC ($P < 0.01$), but the association between educational level and declines on BVRT ($P = 0.40$), TMTB ($P = 0.06$), and MMSE ($P = 0.09$) were smaller in magnitude and not statistically significant at a threshold of $\alpha = 0.05$.

Figures 2 and 3 show the quantile regression coefficients across quantiles, from the 20th to the 80th. In these figures, the plotted values are quantile regression coefficients for the main effects of the education term on the baseline level (predicted for a respondent 65 years of age at baseline) and interactions between the education term and decades of follow-up. (We used decades so baseline and level coefficients were on similar scales.) The association between parental educational level and predicted baseline score on the ISAAC showed a moderate attenuation from quantiles 20 to 80 (Figure 2), suggesting a possible ceiling effect. This pattern prevailed for every outcome, with regression coefficients for baseline performance consistently larger at the 20th percentile than at the 70th or 80th percentile. For example, the mean predicted baseline ISAAC score was 0.59 points higher in the group with high parental educational levels than in the group with low parental educational levels. Similarly, the 80th percentile of the ISAAC score was 0.57 units higher for the high parental education group than for the 80th percentile for persons with low parental education. However, the 20th percentile ISAAC score was 0.75 units higher in the high parental educational level group than in the low parental educational level group.

For ISAAC and BVRT, the associations between parental educational level and the rate of change over the follow-up period were negative (indicating a faster decline associated with higher parental educational level) at low quantiles. For TMTB and MMSE, the coefficients for the association between parental educational level and the rate of change were mostly positive even at low quantiles and did not diverge dramatically from the mixed-model effect estimates. None of the quantile regression coefficients for parental educational level and rate of change were statistically significant at the conventional $\alpha = 0.05$ threshold.

Table 2. Trajectory of Cognitive Test Scores[a] of Participants ($n = 4,480$), Three-City Study, Dijon, France, 1999–2010

Cognitive Test	Random Intercept Models, Unweighted[b]				Random Intercept Models, Inverse Probability Weighted[b]			
	No. of Observations[c]	β	95% CI	*P* Value	No. of Observations[c]	β	95% CI	*P* Value
Isaacs' test	17,072				16,765			
First test encounter		−0.175	−0.209, −0.142	<0.01		−0.190	−0.224, −0.156	<0.01
Baseline age		−0.057	−0.062, −0.052	<0.01		−0.057	−0.062, −0.052	<0.01
Years of follow up		−0.051	−0.058, −0.043	<0.01		−0.057	−0.065, −0.049	<0.01
Benton Visual Retention Test	17,026				16,710			
First test encounter		−0.049	−0.099, 0.001	0.06		−0.065	−0.115, −0.014	0.01
Baseline age		−0.050	−0.054, −0.046	<0.01		−0.050	−0.055, −0.046	<0.01
Years of follow up		−0.022	−0.033, −0.011	<0.01		−0.030	−0.041, −0.018	<0.01
Trail Making Test B (reversed)	12,569				12,186			
First test encounter		−0.092	−0.182, −0.002	0.05		−0.156	−0.250, −0.061	<0.01
Baseline age		−0.037	−0.041, −0.033	<0.01		−0.038	−0.042, −0.034	<0.01
Years of follow up		−0.036	−0.051, −0.020	<0.01		−0.051	−0.068, −0.034	<0.01
Mini-Mental State Examination	17,088				16,795			
First test encounter		−0.186	−0.133, −0.048	<0.01		−0.216	−0.264, −0.167	<0.01
Baseline age		−0.037	−0.041, −0.032	<0.01		−0.038	−0.043, −0.034	<0.01
Years of follow up		−0.071	−0.082, −0.060	<0.01		−0.083	−0.094, −0.072	<0.01

Abbreviation: CI, confidence interval.

[a] All outcomes are expressed as *z* scores using baseline mean and standard deviation.

[b] All models were additionally adjusted for sex and interviewer.

[c] The number of observations differed for the weighted and unweighted models because the weighted models censored individuals at their first nonresponse wave.

Similar patterns were observed for participants' own education (Figure 3). The association between participants' own educational levels and predicted baseline cognitive levels tended to be attenuated at higher quantiles. These patterns suggested that all 4 measures were potentially influenced by ceiling effects, with the smallest bias in ISAAC and the largest in MMSE. However, for every outcome at every quantile, the association between baseline level and education was positive.

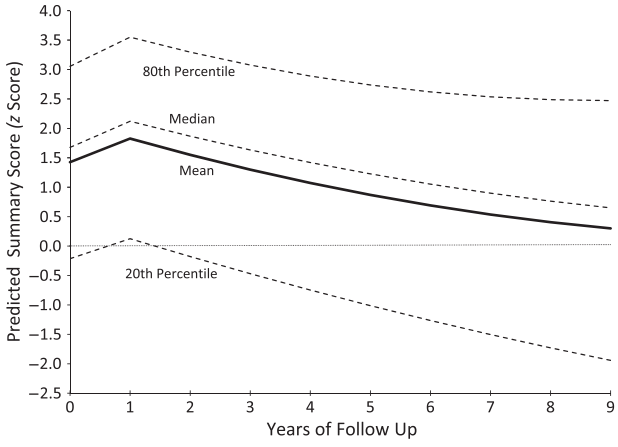

Figure 1. Trajectory of change in summary cognitive score over years of follow-up based on linear mixed (mean) regression models and quantile regression models at the 20th, 50th, and 80th percentiles, Dijon, France, Three-City Study, 1999–2010. Models included sex, baseline age, baseline age squared, first assessment indicator, years of follow up, and years of follow up squared. Predictions were for a female individual 65 years of age at baseline (enrollment) and were inverse probability weighted for survival and drop-out.

The association between participants' own educational level and the rate of change in ISAAC score was negative for all quantiles below the 80th. This association was statistically significant at $\alpha < 0.05$ for the 30th quantile only. For BVRT, TMTB, and MMSE, the coefficients for participants' own educational levels and the rates of change over follow up were consistently small but positive at low quantiles. For MMSE, this association was statistically significant at $\alpha < 0.05$ for all but the 20th and 60th quantiles; coefficients for BVRT and TMTB did not meet statistical significance thresholds.

DISCUSSION

In the present sample of older French adults, relations between participants' own and parental educational levels and baseline cognitive level were large and evident for every cognitive domain examined. The associations between participants' own or parental educational levels and the rates of cognitive change were small, sensitive to model specification, and domain specific. The average decline in ISAAC score was faster among individuals whose parents had a high level of education, but parental educational level was not associated with rate of decline in mean BVRT, TMTB, or MMSE score. Higher levels of participants' own educational

Table 3. Association of Educational Level With Level of and Change in Cognitive Function, Three-City Study, Dijon, France, 1999–2010[a]

	Parental Educational Level of Secondary School or Higher[b]			Participant Educational Level of Secondary School or Higher[b]		
	β	95% CI	*P* Value	β	95% CI	*P* Value
Isaacs' test						
Level at baseline[c]	0.605	0.453, 0.756	<0.01	0.686	0.576, 0.796	<0.01
First test encounter	−0.038	−0.103, 0.028	0.26	−0.027	−0.077, 0.022	0.28
Baseline age[d]	−0.016	−0.029, −0.003	0.02	−0.014	−0.023, −0.004	<0.01
Years of follow up[e]	−0.013	−0.022, −0.003	0.01	−0.006	−0.013, 0.002	0.13
Benton Visual Retention Test						
Level at baseline[c]	0.356	0.216, 0.495	<0.01	0.369	0.267, 0.472	<0.01
First test encounter	−0.010	−0.110, 0.090	0.85	0.043	−0.032, 0.119	0.26
Baseline age[d]	−0.007	−0.018, 0.005	0.25	−0.002	−0.010, 0.006	0.60
Years of follow up[e]	−0.010	−0.025, 0.004	0.17	0.014	0.002, 0.025	0.02
Trail Making Test B (reversed)						
Level at baseline[c]	0.214	0.038, 0.390	0.02	0.262	0.131, 0.393	<0.01
First test encounter	0.056	−0.089, 0.200	0.45	0.120	0.010, 0.230	0.03
Baseline age[d]	−0.003	−0.015, 0.008	0.57	0.003	−0.005, 0.011	0.50
Years of follow up[e]	0.016	−0.006, 0.037	0.15	0.026	0.010, 0.042	<0.01
Mini-Mental State Examination						
Level at baseline[c]	0.442	0.286, 0.599	<0.01	0.529	0.415, 0.643	<0.01
First test encounter	−0.085	−0.180, 0.010	0.08	0.027	−0.045, 0.098	0.46
Baseline age[d]	−0.021	−0.034, −0.008	<0.01	−0.006	−0.016, 0.003	0.21
Years of follow up[e]	−0.003	−0.017, 0.011	0.66	0.022	0.012, 0.033	<0.01

Abbreviation: CI, confidence interval.

[a] Estimates are from inverse probability weighted random intercepts models. All models were adjusted for sex and interviewer, plus main effects of all interactions shown. Participants' own education models were adjusted for parental education main effects and interactions. Parental education models were not adjusted for participants' own education. All outcomes are expressed as *z* scores using baseline mean and standard deviation.

[b] Secondary school attendance corresponds to at least 9 years of schooling unless the ninth year is the completion of a short technical degree.

[c] Level at baseline is the main effect of the education term, representing the mean difference in predicted level for individuals with high and low levels of education at baseline (for a respondent enrolled at 65 years of age).

[d] The coefficient for baseline age is from the interaction of educational level and baseline age (centered so 0 represents age 65 years).

[e] The coefficient for years of follow up is from the interaction of years of follow up and educational levels.

attainment were associated with slightly slower mean declines in BVRT, TMTB, and MMSE scores and nonsignificantly faster declines in ISAAC score. Quantile regression coefficients suggested that the potential benefits of elevated parental and participant education may be incorrectly estimated because of ceiling effects on the outcome measures but generally showed patterns similar to those of the mean-based regression models: slightly faster declines in ISAAC score associated with parental educational level and slightly slower declines in TMTB and MMSE scores associated with participants' own educational level. Differences in rates of decline across participants' or parents' educational levels, although in some cases statistically significant, were very small in absolute magnitude.

Little prior work has examined the association between parental education and the rate of cognitive change. Parents shape children's early cognitive environments; parental education may thus be especially important for neurologic development (38). Our results suggest that among the elderly, high parental educational levels predict substantial advantages in the beginning level but a slightly faster decline in verbal fluency. Our findings add to a growing body of research indicating that educational background does not considerably modify the rate of cognitive change and for some cognitive domains predicts faster decline (14–20). We expand on prior work by implementing adjustments for selective survival and loss to follow up and examining quantile regression models to detect bias due to ceiling and floor effects. These technical improvements did not substantively change the results but did suggest that ceiling bias might contribute to the estimated impact of education on rate of change by obscuring changes in high-functioning individuals.

The skills and strategies improved by higher education may be supported by cognitive networks that are affected relatively early in the aging process. For example, prefrontal cortical areas are recruited in verbal memory or fluency tasks to enable strategy formation and utilization (24). Deterioration of the structure and function of the prefrontal cortex is an early feature of brain aging (25). This deterioration might not severely harm test performance among elderly persons with a low level of education because they did not rely heavily on strategy use for verbal fluency even

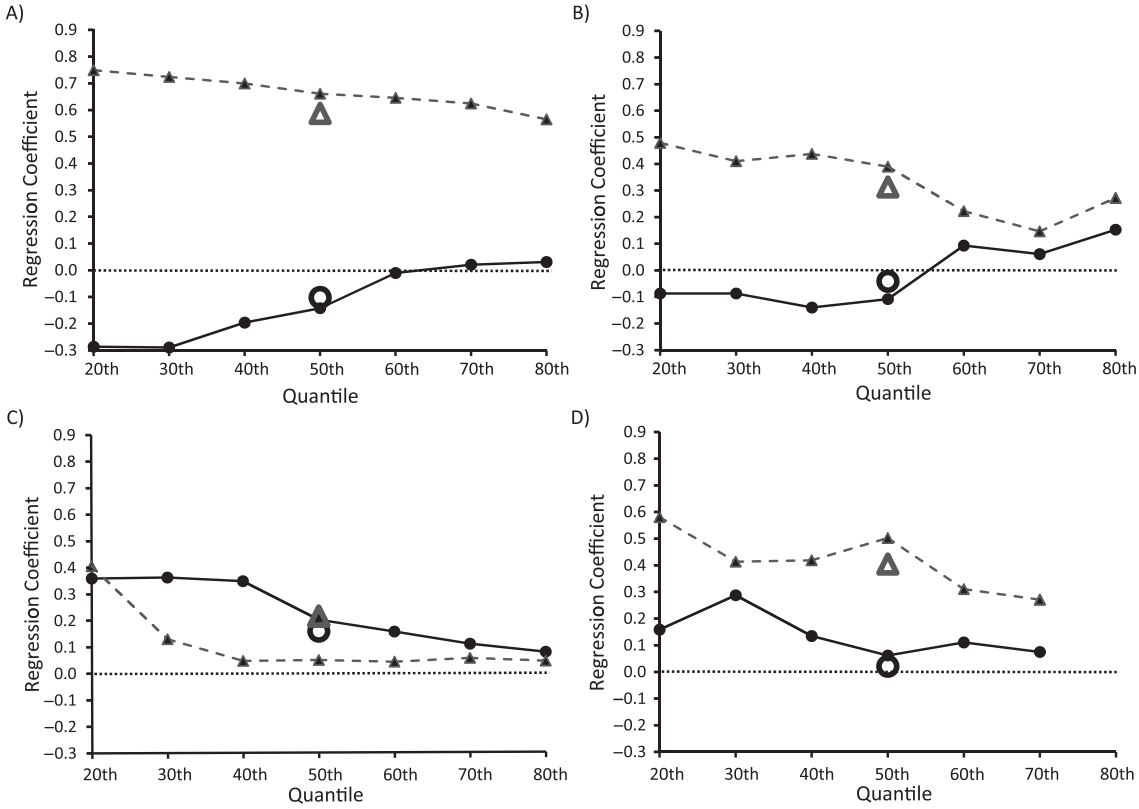

Figure 2. Parental educational level quantile regression coefficients from the 20th to 80th percentiles for A) the Isaacs' test, B) Benton Visual Retention Test, C) Trail Making Test B reversed, and D) Mini-Mental State Examination, Dijon, France, Three-City Study, 1999–2010. The dotted line connecting triangles shows differences by parental educational level in the 20th–80th percentiles of cognitive level at baseline. The solid line with solid circles shows predicted differences by parental educational level in the predicted rate of change per decade based on changes over the follow-up period at the 20th–80th percentiles of cognitive score. For all outcomes, lower quantiles corresponded to worse test performance. Models were also adjusted for sex, baseline age, first assessment indicator, interaction of parental educational level with baseline age, and interaction of parental educational level with first assessment. Predictions are for an individual who was 65 years of age at baseline (enrollment). For comparison, coefficients from random-intercept mixed models (contrasting mean values instead of quantiles) showing difference in predicted baseline score (large circle) and rate of change per decade (large triangle) by parental educational level for the same reference group are also shown on the plots. Models were inverse probability weighted for survival and drop-out.

in youth. In contrast, as strategy use becomes increasingly difficult for individuals with higher levels of education, their performances on fluency tests will deteriorate. This hypothesis is consistent with findings from some prior studies and our finding of a faster decline in the ISAAC score, a measure of category fluency associated with verbal skills and executive function, among persons with higher parental educational levels (15, 16, 21).

Education may nonetheless confer active reserve or compensatory capacity by facilitating recruitment of alternative networks after neurologic injury. These 2 processes—deterioration of strategy-related brain regions and flexible recruitment of alternative networks among persons with high cognitive reserve—may occur simultaneously, with offsetting consequences.

Associations between education and dementia and related conditions have been well established (39). Dementia manifests because pathological processes degrade prior functioning; this manifestation could potentially be delayed by compensatory processes or plasticity. Our findings suggest that education has very little influence on cognitive change and thus is unlikely to strongly influence either neurodegenerative or compensatory processes. Education may nonetheless delay dementia manifestation because it improves cognitive skills acquired in childhood or because the diagnostic criteria for dementia are biased with respect to education (40, 41).

Our study has several limitations. We interpreted the associations cautiously because most were small and inconsistent across model specifications. A more general concern is that growth curve models can be seriously biased by scaling problems in the dependent variable. Cognitive scale scores, even when converted to *z* scores as we did here, are not necessarily scaled with equally spaced intervals. Ceiling or floor effects (such as those likely to occur for the MMSE score) introduce such skewing. We believe ceilings account for the inconsistent quantile regression coefficients. Floor effects are also a concern, because individuals with more education presumably have a greater distance to decline before hitting a ''floor'' of minimum possible human cognitive ability. However, if there were influential floors, we would expect the coefficients for the impact of education on

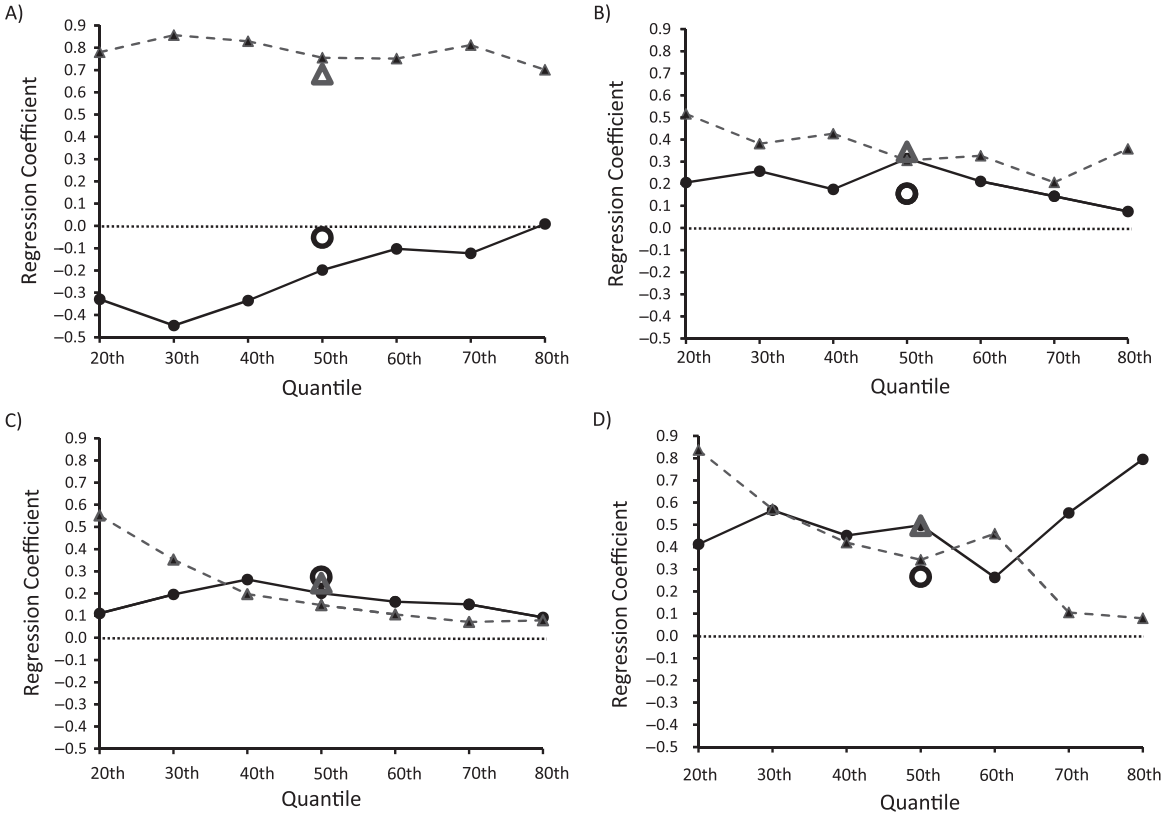

Figure 3. Quantile regression coefficients for participants' educational levels from the 20th to 80th percentiles for A) the Isaacs' test, B) Benton Visual Retention Test, C) Trail Making Test B reversed, and D) Mini-Mental State Examination, Dijon, France, Three-City Study, 1999–2010. The dotted line connecting triangles shows predicted differences by participants' own educational levels in the 20th–80th percentiles of cognitive level at baseline. The solid line with solid circles shows differences by participants' own educational levels in predicted rate of change per decade based on changes over the follow-up period at the 20th–80th percentiles of cognitive score. For all outcomes, lower quantiles corresponded to worse test performance. Models were also adjusted for sex, baseline age, first assessment indicator, interaction of parental educational level with baseline age, interaction of parental educational level with first assessment, interaction of parental educational level with years of follow up, interaction of participants' own educational level with baseline age, and interaction of participants' own educational level with first assessment indicator. Predictions are for an individual who was 65 years of age at baseline (enrollment). For comparison, coefficients from random-intercept mixed models (contrasting mean values instead of quantiles) showing difference in predicted baseline score (large circle) and rate of change per decade (large triangle) by the participants' own educational levels for the same reference group are also shown on the plots. Models were inverse probability weighted for survival and drop-out.

baseline level to be attenuated at lower quantiles. That is not what we found (Figures 2 and 3). Similarly, regression to the mean, a concern in studies of patient samples, should not apply in population samples such as those of the Three-City Study. The Three-City Study sample was not conditioned on baseline performance, and we did not introduce any baseline adjustment in our analyses.

Another limitation is potential bias due to selective participation, drop-out, or death in the Three-City Study. Educational level and risk of cognitive decline may each affect the chances of being observed at baseline and in each wave. We attempted to ameliorate this bias using IPWs. The weighted and unweighted coefficients were generally similar, which suggests that this was not a major source of bias. However, these models assume missingness is random and conditional on the variables included in the weighting models; this assumption is unverified. Finally, our study is in a single French community and may not be generalizable to other populations.

Higher parental educational levels predicted faster declines in verbal fluency, whereas participants' own educational levels were associated with slightly slower declines on other assessments. The magnitude of the associations between educational background and level of cognitive performance dwarfs plausible differences in rates of change. The results, in combination with prior evidence suggesting null or very small relations (14–20), suggest that population increases in educational attainment may reduce the incidence of impaired performance (e.g., performance below any specified threshold) but are unlikely to substantially reverse or slow the functional consequences of neurodegenerative diseases.

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Author affiliations: Department of Society, Human Development, and Health, Harvard School of Public Health,

Boston, Massachusetts (M. Maria Glymour); Université Bordeaux, U708, Bordeaux, France (Christophe Tzourio, Carole Dufouil); INSERM, Neuroepidemiology U708, Bordeaux, France (Christophe Tzourio, Carole Dufouil); and INSERM, ISPED, CIC-EC7, Bordeaux, France (Carole Dufouil).

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